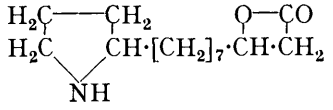
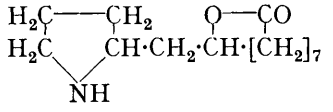
140. *Constitution of Carpaine. Part III.*

By G. Barger, Robert Robinson, and T. S. Work.

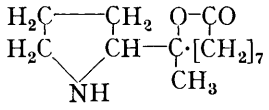
Carpaine is a lactone and is hydrolysed to carpamic acid (Barger, J., 1910, **97**, 466), from which the original alkaloid has so far not been regenerated. Oxidation with nitric acid yields azelaic acid, proving the presence of a chain of seven methylene groups (Barger, Girardet, and Robinson, *Helv. Chim. Acta*, 1933, **16**, 90). This led to the suggestion that either a β-lactone ring (as in I) or a much larger lactonic ring (as in II) is present.

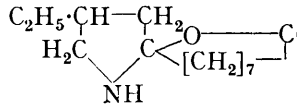
(I.) 

(II.) 

We have now found that carpaine and some of its degradation products contain one *C*-methyl group (estimated by the Kuhn–Roth method). A formula of type (I) and containing such a methyl group could only have six methylene groups between its two rings; this therefore rules out a β-lactone structure, which is also contradicted by the ozonisation of anhydrocarpamic acid (see below). Formula (II) can, however, be readily modified to accommodate a methyl group, since it has a spare carbon atom between the two rings, which we now therefore consider to be joined directly. The large lactone ring also explains our inability to regenerate carpaine from carpamic acid. In assigning a position to the methyl group we take into account the further observation that carpamic acid is a tertiary and not a secondary alcohol. This was already indicated by the observation of Barger, Girardet, and Robinson that carpamic acid, on heating with formaldehyde, merely forms *N*-methylcarpamic acid, whilst pyrrolidyl]propanols, containing a secondary alcoholic group, are transformed to ketones (Hess, *Ber.*, 1913, **46**, 4107).

Additional evidence for the tertiary alcohol group is now provided by the observation that on boiling carpamic acid with potassium dichromate and sulphuric acid a considerable proportion is recovered unchanged, and no keto-acid can be isolated. Accordingly we place the methyl group as in (III), which formula is being used as the basis of synthetic experiments (see the succeeding papers).

(III.) 

(IV.) 

The only arrangement in which the tertiary alcohol group does not involve a methyl group is of type (IV), where two carbon atoms have to be accommodated on the pyrrolidine ring; since they cannot both be *C*-methyl groups, this alternative has been illustrated with an ethyl group in an arbitrary position. Neither of the last two carbon atoms can be in the lactone ring, for this would then yield sebacic rather than azelaic acid. We do not consider a formula of type (IV) very likely; (III) is moreover in accordance with a biochemical origin from proline. In all the above formulæ the lactone ring is represented as attached to an α-position of the pyrrolidine ring; the evidence for this is of two kinds. In the first place one of the α-positions must be substituted, for carpamic acid yields no colour reaction with isatin which, according to Grassmann and von Arnim (*Annalen*, 1935, **519**, 192), is given by pyrrolidine derivatives in which both α-positions are free. In the second place the elimination of the nitrogen atom from carpaine results in substances containing 14 carbon atoms which still have only one *C*-methyl group; if the lactone ring were attached in a β-position, a second *C*-methyl would be generated by the opening of the pyrrolidine ring. This opening has been brought about both by violent reduction and by exhaustive methylation. When carpamic acid is heated with hydriodic acid and phosphorus at 320°, the nitrogen is eliminated as ammonia and a *hydrocarbon* results, probably $(CH_2)_n$. From a molecular weight determination and the fact that myristic acid by similar treatment yields tetradecane, without decarboxylation (Krafft, *Ber.*, 1882, **15**, 1700), we believe the hydrocarbon from carpaine to be $C_{14}H_{28}$ or possibly $C_{14}H_{30}$. It contains only one *C*-methyl group. (The formula $C_{14}H_{28}$ would involve the formation of a ring, not readily explained.) The exhaustive methylation of carpaine, followed by catalytic reduction, yielded a lactone, which was hydrolysed to an *acid*, $C_{14}H_{28}O_3$, with one *C*-methyl group. It was characterised as the *p*-phenylphenacyl ester and its synthesis is being attempted.

Whilst the direct dehydration of carpamic acid, with the formation of a double bond, yielded no satisfactory product, this end was achieved indirectly by successive treatment with phosphorus pentachloride and potassium hydroxide. The unsaturated anhydrocarpamic acid so obtained was reduced to *deoxycarpamic acid*, and was also oxidised by ozone and by permanganate. The ozonisation product, obtained in minute amount, was an acid with an equivalent weight corresponding to $CH_3{\cdot}CO{\cdot}[CH_2]_7{\cdot}CO_2H$, in any case monobasic. Formula (I) would require the formation of oxalic or malonic acid and an amphoteric substance. Oxidation of anhydrocarpamic acid with permanganate yielded azelaic and other acids.

Experimental.

The carpaine used in these experiments was obtained from 100 kg. of dried old leaves of *Carica Papaya*, which were extracted with 80% alcohol containing 0·5% of acetic acid. The yield (0·018%) was extremely disappointing; young leaves contain very much more alkaloid.

C-Methyl groups in carpamic acid were estimated by the Kuhn–Roth chromic acid method by Dr. H. Roth (Found: 0·99, 1·00, 1·01, 1·02).

Oxidation of Carpamic Acid by Chromic Acid.—Carpamic acid hydrochloride (0·8 g.) was dissolved in water, and the calculated quantity of potassium dichromate in sulphuric acid (Beckmann's mixture) added; after heating for 1 hour, the dichromate had been used up. After removal of inorganic matter an oil was obtained, a solution of which in the minimum quantity of hydrochloric acid yielded crystals on evaporation; these, recrystallised from acetone, had m. p. 157—158°, and m. p. 160° when mixed with carpamic acid hydrochloride; 40% of the starting material was thus recovered unchanged. The small amount of residual uncrystallisable oil gave no reactions for a ketone.

Reduction of Carpamic Acid.—Carpamic acid hydrochloride (0·5 g.), red phosphorus (0·5 g.), and hydriodic acid (5·0 g., *d* 1·7) were heated for 7 hours at 320—330°. After dilution with water and extraction with ether, the ethereal solution was freed from iodine with copper powder. On evaporation an oil was left, which distilled in a high vacuum at about 90° and remained liquid. Yield, 30—80 mg. (Found: C, 86·0; H, 13·9; *M*, by micro-Rast, 192, 185. $C_{14}H_{28}$ requires C, 85·7; H, 14·3%; *M*, 196). Myristic acid, treated in the same way, yielded a very similar *hydrocarbon* (Found: C, 84·6; H, 15·5. $C_{14}H_{30}$ requires C, 84·8; H, 15·2%). The refractive indices, kindly determined by Dr. E. G. V. Percival, were $n_D^{17°}$ 1·4325 for the hydrocarbon from carpaine and 1·4320 for that from myristic acid. The *C*-methyl found in the hydrocarbon from carpaine was 0·93, 0·88 (by Dr. H. Roth). In the aqueous solution, which was extracted with ether, ammonia was recognised by Nessler's reagent.

Exhaustive Methylation.—Carpaine (4 g.) was dissolved in methyl alcohol and heated at 100° for 12 hours with excess of methyl iodide. The quaternary iodide was decomposed with silver carbonate, and the ether-soluble portion of the resulting oil treated again with methyl iodide in the same way. The quaternary carbonate was heated at 150° in a high vacuum until frothing ceased, and then distilled (bath 160—180°). The colourless oily distillate was heated with methyl iodide for 16 hours at 100°, and the carbonate distilled (bath 160—190°). The distillate (2·1 g.) was reduced catalytically with platinum oxide and hydrogen, and the resulting oil separated into a neutral (0·45 g.) and a basic fraction (1·0 g.), both soluble in ether. The latter, treated as before, yielded a further 0·05 g. of neutral oil. The total (0·5 g.) was boiled with alcoholic potassium hydroxide for 4 hours. On acidification and extraction with ether a crystalline acid was obtained, melting indefinitely at 20—25° (Found : C, 69·0; H, 11·2; equiv. by titration, 249. $C_{14}H_{28}O_3$ requires C, 68·9; H, 11·5%; equiv., 244). The acid contains one *C*-methyl group (Found : 0·35 by Dr. H. Roth, who suggests that in an open vessel some methyl *n*-butyl ketone escapes unoxidised. Myristic acid gave a negative result). The *hydroxyisomyristic acid* yielded a crystalline *p*-phenylphenacyl ester.

Attempted Direct Dehydration of Carpamic Acid.—The acid was recovered in almost quantitative yield after heating at 170° for 10 hours with concentrated sulphuric and glacial acetic acids (2 : 1). Treatment with zinc chloride in acetic acid yielded an uncrystallisable oil.

Chlorination of Ethyl N-Methylcarpamate.—This ester (0·5 g.) (Barger, Girardet, and Robinson) was dissolved in ether and treated with slightly more than the theoretical quantity of thionyl chloride. After standing overnight, the ethereal solution was washed with aqueous sodium carbonate, and the oil, left on evaporation, was distilled in a high vacuum. The distillate (0·2 g.) set to a crystalline mass melting rather indefinitely at about 30° (Found : Cl, 12·0. $C_{17}H_{32}O_2NCl$ requires Cl, 11·2%).

Indirect Dehydration of Carpamic Acid. Anhydrocarpamic and Deoxycarpamic Acids.—Carpamic acid hydrochloride (1·0 g.) was dissolved in the minimum quantity of phosphorus oxychloride and excess of the pentachloride was added. After heating for 2 hours on the water-bath the oxychloride was removed in a vacuum. The residue was boiled for 4 hours with 25% potassium hydroxide in methanol, cooled, made just acid to methyl-red, evaporated to dryness, and extracted with alcohol. Anhydrocarpamic acid was obtained as a non-crystallisable oil and was reduced with platinum oxide in acetic acid; 61 c.c. of hydrogen were absorbed (calc. for 1·0 g. of carpamic acid hydrochloride, 80 c.c.). The *deoxycarpamic acid* crystallised on evaporation; after recrystallisation from acetone–alcohol, it sublimed at 155—160°/1 mm. in needles, m. p. 181°; yield, 200 mg. (Found : C, 69·9; H, 11·4; N, 5·2. $C_{14}H_{27}O_2N$ requires C, 69·7; H, 11·2; N, 5·8%). The solubilities were similar to those of carpamic acid.

Ozonisation of Anhydrocarpamic Acid.—The crude anhydrocarpamic acid, prepared as above from carpamic acid (0·5 g.), was ozonised in aqueous solution. After acidification and extraction with ether the residual acidic oil distilled in a high vacuum (bath 130—140°). The colourless distillate did not crystallise (Found : equiv. by titration, 190. A keto-acid, $CH_3{\cdot}CO{\cdot}[CH_2]_7{\cdot}CO_2H$ requires equiv., 186). After esterification with diazomethane and treatment with ammonia a crystalline substance was obtained in amount too small for further examination.

Oxidation of Anhydrocarpamic Acid with Permanganate.—The crude anhydro-acid from 0·9 g. of carpamic acid hydrochloride was treated in slightly alkaline aqueous solution with 2% potassium permanganate solution; 78 c.c. were decolorised in the cold, and a further 72 c.c. in the course of 2 hours on the water-bath (total, 3·1 oxygen atoms). The solution was filtered, acidified, and extracted with ether. The ethereal extract (*A*) and the acid solution (*B*) were evaporated to dryness. (*A*) yielded an oil, which on distillation at 1 mm. gave (1) a semi-solid mass (bath at 170—190°), m. p. 110—124°, very sparingly soluble in ether; the amount was insufficient for purification (? impure suberic acid; cf. Barger, Girardet, and Robinson); (2) a crystalline solid (bath 190—210°). After five crystallisations from water the m. p. was constant at 103—104° and the mixture with authentic azelaic acid (m. p. 105—106°) melted at 103—104·5°. The quantity was insufficient for analysis. The residue from (*B*) was separated from inorganic matter by extraction with alcohol and distilled at 1 mm. (bath 150—180°). A colourless nitrogen-free oil was obtained, soluble in water, sparingly in ether, and acidic. On treatment with ammonia and distillation with zinc dust the pyrrole reaction with pine wood was obtained (succinic acid ?).

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